Applicants respectfully submit that no new matter has been added by the foregoing amendments.

Common Ownership

The present application, Serial No. 09/826,509, (the "509 application"), was filed on April 5, 2001. The '509 application and U.S. Patent No. 6,150,393 to Behan *et al.* were, at the time of the invention of the subject matter of '509 application, owned by or subject to an obligation of assignment to Arena Pharmaceuticals, Inc.

Rejections under 35 U.S.C. §112, second paragraph

Claim 103 is rejected under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. The Office Action alleges that it is unclear what the phrase "the parallel agonists" means. While Applicants disagree with the Office Action, and assert that those of skill in the art would know what the cited phrase means, solely in an effort to advance prosecution claim 103 has been amended to delete the word "parallel", thus rendering the rejection in this regard moot.

The Office also alleges that the methods set forth by the claim

> ...do not necessarily achieve the goal of identifying a compound having an activity selected from the group consisting of inverse agonist, parallel agonist, and partial agonists, as defined by the claim preamble. Additional steps need to be added.

Office Action at page 4. Applicants respectfully disagree with the Office Aciton.

The proper inquiry, when determining whether a claim satisfies the requirements of 35 U.S.C. § 112, second paragraph, is a determination "whether those skilled in the art would understand what is claimed when the claim is read in light of the specification." *Orthokinetics Inc. v. Safety Travel Charis, Inc.*, 1 U.S.P.Q.2d 1081, 1088 (Fed. Cir. 1986). Thus, if those skilled in the art can understand what is claimed when the claim is read in light of the specification, a rejection under 35 U.S.C. § 112, second paragraph, is inappropriate.

Applicants respectfully assert that the art-skilled would readily understand claim 103. Claim 103 as amended recites a method for directly identifying a non-endogenous

compound that is an agonist, inverse agonist, or partial agonist to a non-endogenous constitutively activated version of known G protein-coupled receptor (GPCR). The method comprises four steps as described in the claim. The description and examples in the specification of the present application show how to follow these steps to determine whether or not the non-endogenous compound is an agonist, inverse agonist, or partial agonist.

Significantly, the Office Action has provided no evidence that one of skill in the art would fail to understand what is claimed, or that those of skill in the art, following the steps recited in claim 103, would be unable to directly identify compounds as an agonist, inverse agonist, or partial agonist. Accordingly, the present rejection is inappropriate.

Additionally, to the extent that the Office Action intended to base its rejection on an assertion that those of ordinary skill would not absolutely identify a compound having one of the recited activities in every case, Applicants respectfully point out that such an argument improperly presupposes the very knowledge that the claimed method is intended to elicit. If a compound subjected to the claimed method is not an agonist, inverse agonist, or partial agonist, then it simply will not be identified as such. The patent laws do not require that every candidate compound that could be subjected to a claimed method will be active. Rather, as discussed above, all that is required under 35 U.S.C. § 112, second paragraph is that those of skill in the art understand what is being claimed. And in the absence of any evidence contravening Applicants' assertions above that one of skill in the art would readily be able to do so, Applicants respectfully request the reconsideration and withdrawal of this rejection.

Rejections under 35 U.S.C. §102(b)

Claims 101-104 stand rejected under 35 U.S.C. § 102 for alleged anticipation by Herrick-Davis *et al.*, (Annals of the New York of Academy of Sciences 861:140-145, 1998, hereinafter referred to as the "Herrick-Davis reference"). The Office Action alleges that Herrick-Davis teaches constitutively activating a 5-HT_{2C} receptor and the use of such constitutively activated receptors in methods for identifying agonists, partial agonists, and antagonists. Applicants respectfully disagree with the rejection.

The standard for anticipation under § 102(b) is one of strict identity. An anticipation rejection requires a showing that each limitation of a claim be found in a single reference. *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984).

The Herrick-Davis reference fails to teach each limitation of claims 101-104. The Herrick-Davis reference discusses a mutation of the 5-HT_{2C} receptor which is intended to constitutively activate the receptor, and describes experiments performed to determine that the mutation achieved the constitutive activation. Herrick-Davis, however, fails to teach methods for identifying a non-endogenous compound as an agonist, partial agonist, or inverse agonist by contacting the non-endogenous candidate compound with a non-endogenous, constitutively activated GPCR or determining the activity of these compounds (*e.g.* as agonists, inverse agonists, or antagonists). The Herrick-Davis reference merely discusses the use of compounds previously known to be either agonists or antagonists of the receptor, and uses the previously known compounds as tools to determine ***whether or not the mutant 5-HT_{2C} receptor is constitutively active***. Herrick-Davis ***does not*** teach or suggest the use of the constitutively active receptor ***to determine the activity of the compound.*** Therefore, Herrick-Davis reference fails to anticipate claim 103.

Furthermore, as claims 101, 102, 104, and 105 depend from claim 103, the Herrick-Davis reference also fails to anticipate these claims as well. In this regard, Applicants note that claim 105 recites that the receptor have the amino acid sequence of SEQ ID NO:449. Herrick-Davis fails to teach or even suggest the amino acid sequence of SEQ ID NO:449.

In view of the foregoing, Applicants respectfully request the reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b).

Rejections under 35 U.S.C. § 102(e)

Claims 101-104 stand rejected under 35 U.S.C. § 102(e) over Behan *et al* (U.S. Patent No. 6,150,393; "the 393 patent"). The Office Action alleges that the 393 patent teaches non-endogenous, constitutively active forms of 5-HT_{2a} and 5-HT_{2c} receptors and the use of such receptors to identify agonists, inverse agonists, and antagonists of said

receptor. Applicants respectfully traverse the rejection, as the 393 patent is not prior art against the claims of the present application.

Applicants attach hereto a "Declaration of Chen W. Liaw". In the Declaration, Dr. Liaw states that "to the extent that the 393 patent discloses the subject matter relating to human 5HT-2a and 5-HT-2c serotonin receptors claimed in the present application, I hereby declare that I am the sole inventor of any subject matter so disclosed". (Declaration at ¶3). Dr. Liaw further states that the other named inventors of the 393 patent did not conceive the subject matter disclosed in the 393 patent relating to constitutively activated forms of human 5HT-2a and 5-HT-2c serotonin receptors. (Declaration at ¶4). Therefore, pursuant to MPEP §715.01(b), the 393 patent is removed as prior art.

In view of the foregoing, Applicants respectfully request the reconsideration and withdrawal of this rejection.

Rejections under 35 U.S.C. § 103 (a)

Claim 105 stands rejected under 35 U.S.C. § 103(a) for alleged unpatentability over Herrick-Davis *et al.* or the 393 patent in view of Kohen *et al.* (J. Neurochem. 66:47-56, 1996, hereinafter referred to as the "Kohen reference"). The Office Action alleges that both the Herrick-Davis reference and the 393 patent teach a method for identifying agonists, partial agonists, and inverse agonists, and that the Kohen reference discloses a constitutively active 5-HT_6 receptor which differs from the sequence of SEQ ID NO:449 by a single amino acid, and concludes that it would have been obvious for one skilled in the art to combine the references to make the non-endogenous, constitutively activated forms of the human 5-HT_6 serotonin receptor from the cDNA sequence taught by the Kohen reference using the approaches discussed in the Herrick-Davis reference, and to include such mutants in the methods of the Herrick-Davis reference. The Office Action asserts that motivation for combining the references is provided by the teaching of the 393 patent, referring to the last paragraph of column 1. Applicants respectfully request reconsideration of the rejection, as the combination of the art would not produce the presently claimed invention, and the reference relied upon for providing motivation for combining the cited art is not prior art against the present claims.

Claim 105, which ultimately depends from claim 103, recites the method of claim 103 wherein the receptor is a known serotonin receptor which has an amino acid sequence selected from several SEQ ID NOs, including SEQ ID NO:449. However, as discussed above, the Herrick-Davis reference fails to teach or suggest methods for identifying a non-endogenous compound as an agonist or inverse agonist of a non-endogenous, constitutively active receptor. Herrick-Davis further fails to teach such a method wherein the receptor has the amino acid sequence of SEQ ID NO:449, instead only discussing a constitutively active 5-HT_{2C} receptor (in this regard, Applicants respectively point out that SEQ ID NO:449 represents a 5-HT_6 receptor - see page 66 of application as filed).

The Kohen reference fails to compensate for the deficiencies of Herrick-Davis. Kohen fails to teach or even suggest methods for identifying a non-endogenous compound as an agonist, partial agonist or inverse agonist of a non-endogenous, constitutively active receptor. And, as admitted by the Office Action, the Kohen does not teach such a method wherein the receptor has the amino acid sequence of SEQ ID NO:449, but rather discusses a constitutively active 5-HT_6 receptor, which differs from the sequence of SEQ ID NO:449. Thus, even if combined, the art does not produce Applicants' claimed invention.

Further, with the exception of the 393 patent (*see infra*), the Office Action has pointed to no legally sufficient motivation in the cited art to make its asserted combination. The Office Action further has not provided any evidence that those of ordinary skill in the art would have **any** expectation of success for combining the references, much less a ***reasonable*** expectation of success required under the patent laws.

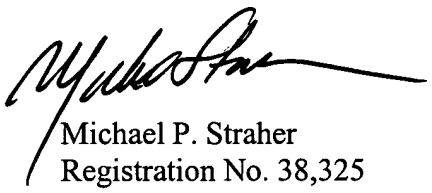
The Office Action states that motivation for combining the cited art is found in the 393 patent. However, as discussed above, the 393 patent is not prior art under 35 U.S.C. § 103(a) because the present application and the Behan reference are commonly owned and the present application has a filing date after November 29, 2000. Additionally, in view of the Declaration of Dr. Liaw attached hereto and discussed above, the 393 patent also is not prior art under 35 U.S.C. § 102(e) or §103. Accordingly, the 393 patent cannot form the basis of an obviousness rejection, and cannot provide the motivation for combining the art as asserted by the Office Action.

Applicants respectfully assert that the Office Action has failed to establish a *prima facie* case of obviousness for at least the reasons set forth above. The Office Action has failed to provide any legally sufficient motivation to combine the cited art. And even if such motivation were to exist, the asserted combination would not produce the claimed invention, and the Office Action has pointed to nothing that would impel the ordinarily skilled artisan to alter the hypothetical combination of the art to achieve the presently claimed invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. § 103(a).

Attached hereto is a marked-up version of the changes made to the application by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

The foregoing represents a *bona fide* attempt to advance the present application to allowance. Applicants respectfully invite the Office to contact the undersigned at (215) 564-8950 to discuss any issues unresolved by this response. A Notice of Allowance is earnestly solicited.

Respectfully submitted,



Michael P. Straher
Registration No. 38,325

Date: August 22, 2002

WOODCOCK WASHBURN LLP
One Liberty Place - 46th Floor
Philadelphia, PA 19103
(215) 568-3100

Attachments:

"Version with markings to show changes made"
" Declaration of Chen W. Liaw"

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification

Please amend the specification as follows:

Please amend the first paragraph on page 1 as follows:

-- This patent application claims priority from U.S. Provisional Application Number 60/195,747, filed with the United States Patent and Trademark Office on April 7, 2000, [; and is related to U.S. Serial Number 09/170,496, filed with the United States Patent and Trademark Office on October 13, 1998, each of] which is incorporated in its entirety by reference. --

On page 12, immediately following line 5, please insert the following new paragraph:

-- The present application is related to U.S. Patent Application Ser. No. 09/170,496, filed October 13, 1998, which is incorporated by reference in its entirety. --

Please amend the second full paragraph on page 49 that precedes Table F as follows:

-- Preparation of non-endogenous known GPCRs is preferably accomplished by using [Transformer Site-Directed™] TRANSFORMER SITE-DIRECTED™ Mutagenesis Kit (Stratagene, according to manufacturer's instructions) or [QuikChange Site-Directed™] QUIKCHANGE SITE-DIRECTED™ Mutagenesis (Clontech). Endogenous GPCR is preferably used as a template and two mutagenesis primers utilized, as well as, most preferably, a lysine mutagenesis oligonucleotide and a selection marker oligonucleotide (SEQ.ID.NO.: 252; included in Stratagene's kit). For convenience, the codon mutation incorporated into the known GPCR and the respective oligonucleotides are noted, in standard form (Table F): --

Please amend the paragraph bridging pages 71 and 72 as follows:

-- A less costly but equally applicable alternative has been identified which also meets the needs of large scale screening. [Flash plates™] FLASH PLATES™ and [Wallac™] WALLAC™ scintistrips may be utilized to format a high throughput [^{35}S]GTPγS binding assay. Furthermore, using this technique, the assay can be utilized for known GPCRs to simultaneously monitor tritiated ligand binding to the receptor at the same time as monitoring the efficacy via [^{35}S]GTPγS binding. This is possible because the Wallac beta counter can switch energy windows to look at both tritium and ^{35}S-labeled probes. This assay may also be used to detect other types of membrane activation events resulting in receptor activation. For example, the assay may be used to monitor ^{32}P phosphorylation of a variety of receptors (both G protein coupled and tyrosine kinase receptors). When the membranes are centrifuged to the bottom of the well, the bound [^{35}S]GTPγS or the ^{32}P-phosphorylated receptor will activate the scintillant which is coated of the wells. [Scinti®] SCINTI® strips (Wallac) have been used to demonstrate this principle. In addition, the assay also has utility for measuring ligand binding to receptors using radioactively labeled ligands. In a similar manner, when the radiolabeled bound ligand is centrifuged to the bottom of the well, the scintistrip label comes into proximity with the radiolabeled ligand resulting in activation and detection. --

Please amend the paragraph on page 72 that begins with "A Flash Plate" and ends with "express the receptors" as follows:

-- A [Flash Plate™] FLASH PLATE™ Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) designed for cell-based assays can be modified for use with crude plasma membranes. The Flash Plate wells contain a scintillant coating which also contains a specific antibody recognizing cAMP. The cAMP generated in the wells was quantitated by a direct competition for binding of radioactive cAMP tracer to the cAMP antibody. The following serves as a brief protocol for the measurement of changes in cAMP levels in membranes that express the receptors. --

Please amend the paragraph bridging pages 72 and 73 as follows:

-- Transfected cells are harvested approximately three days after transfection. Membranes were prepared by homogenization of suspended cells in buffer containing 20mM HEPES, pH 7.4 and 10mM $MgCl_2$. Homogenization is performed on ice using a Brinkman [Polytron™] POLYTRON™ for approximately 10 seconds. The resulting homogenate is centrifuged at 49,000 X g for 15 minutes at 4°C. The resulting pellet is then resuspended in buffer containing 20mM HEPES, pH 7.4 and 0.1 mM EDTA, homogenized for 10 seconds, followed by centrifugation at 49,000 X g for 15 minutes at 4°C. The resulting pellet can be stored at -80°C until utilized. On the day of measurement, the membrane pellet is slowly thawed at room temperature, resuspended in buffer containing 20mM HEPES, pH 7.4 and 10mM $MgCL_2$ (these amounts can be optimized, although the values listed herein are preferred), to yield a final protein concentration of 0.60mg/ml (the resuspended membranes were placed on ice until use). –

Please amend the paragraph on page 73 that begins with "cAMP standards and" and ends with "assay plate" as follows:

-- cAMP standards and Detection Buffer (comprising 2 μCi of tracer [^{125}I cAMP (100 μl)] to 11 ml Detection Buffer) are prepared and maintained in accordance with the manufacturer's instructions. Assay Buffer is prepared fresh for screening and contained 20mM HEPES, pH 7.4, 10mM $MgCl_2$, 20mM (Sigma), 0.1 units/ml creatine phosphokinase (Sigma), 50 μM GTP (Sigma), and 0.2 mM ATP (Sigma); Assay Buffer can be stored on ice until utilized. The assay is initiated by the addition of 50μL of assay buffer followed by addition of 50 μL of membrane suspension to the NEN Flash Plate. The resultant assay mixture is incubated for 60 minutes at room temperature followed by addition of 100 μL of detection buffer. Plates are then incubated an additional 2-4 hours followed by counting in a Wallac [MicroBeta™] MICROBETA™ scintillation counter. Values of cAMP/well are extrapolated from a standard cAMP curve that is contained within each assay plate. –

Please amend the paragraph bridging pages 74 and 75 as follows:

-- A [Flash Plate™] FLASH PLATE™ Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) designed for cell-based assays can be modified for use with

crude plasma membranes. The Flash Plate wells can contain a scintillant coating which also contains a specific antibody recognizing cAMP. The cAMP generated in the wells can be quantitated by a direct competition for binding of radioactive cAMP tracer to the cAMP antibody. The following serves as a brief protocol for the measurement of changes in cAMP levels in whole cells that express the receptors. --

Please amend the paragraph bridging pages 77 and 78 as follows:

-- A method to detect Gs stimulation depends on the known property of the transcription factor CREB, which is activated in a cAMP-dependent manner. A [PathDetect™] PATHDETECT™ CREB trans-Reporting System (Stratagene, Catalogue # 219010) can utilized to assay for Gs coupled activity in 293 or 293T cells. Cells are transfected with the plasmids components of this above system and the indicated expression plasmid encoding endogenous or mutant receptor using a Mammalian Transfection Kit (Stratagene, Catalogue #200285) according to the manufacturer's instructions. Briefly, 400 ng pFR-Luc (luciferase reporter plasmid containing Gal4 recognition sequences), 40 ng pFA2-CREB (Gal4-CREB fusion protein containing the Gal4 DNA-binding domain), 80 ng pCMV-receptor expression plasmid (comprising the receptor) and 20 ng CMV-SEAP (secreted alkaline phosphatase expression plasmid; alkaline phosphatase activity is measured in the media of transfected cells to control for variations in transfection efficiency between samples) are combined in a calcium phosphate precipitate per the Kit's instructions. Half of the precipitate is equally distributed over 3 wells in a 96-well plate, kept on the cells overnight, and replaced with fresh medium the following morning. Forty-eight (48) hr after the start of the transfection, cells are treated and assayed for, e.g., luciferase activity. --

Please amend the paragraph bridging pages 80 and 81 as follows:

-- A method to detect Gq stimulation depends on the known property of Gq-dependent phospholipase C to cause the activation of genes containing AP1 elements in their promoter. A [Pathdetect™] PATHDETECT™ AP-1 cis-Reporting System (Stratagene, Catalog # 219073) can be utilized following the protocol set forth above with respect to the CREB reporter assay, except that the components of the calcium phosphate

precipitate were 410 ng pAP1-Luc, 80 ng pCMV-receptor expression plasmid, and 20 ng CMV-SEAP. --

Please amend the paragraph on page 81 between headings 4 and 5 as follows:

-- One method to detect Gq stimulation depends on the known property of Gq-dependent phospholipase C to cause the activation of genes containing serum response factors in their promoter. A [Pathdetect™] PATHDETECT™ SRF-Luc-Reporting System (Stratagene) can be utilized to assay for Gq coupled activity in, e.g., COS7 cells. Cells are transfected with the plasmid components of the system and the indicated expression plasmid encoding endogenous or non-endogenous GPCR using a [Mammalian Transfection™] MAMMALIAN TRANSFECTION™ Kit (Stratagene, Catalogue #200285) according to the manufacturer's instructions. Briefly, 410 ng SRF-Luc, 80 ng pCMV-receptor expression plasmid and 20 ng CMV-SEAP (secreted alkaline phosphatase expression plasmid; alkaline phosphatase activity is measured in the media of transfected cells to control for variations in transfection efficiency between samples) are combined in a calcium phosphate precipitate as per the manufacturer's instructions. Half of the precipitate is equally distributed over 3 wells in a 96-well plate, kept on the cells in a serum free media for 24 hours. The last 5 hours the cells are incubated with 1mM Angiotensin, where indicated. Cells are then lysed and assayed for luciferase activity using a [Luclite™] LUCLITE™ Kit (Packard, Cat. # 6016911) and "Trilux 1450 Microbeta" liquid scintillation and luminescence counter (Wallac) per the manufacturer's instructions. The data can be analyzed using [GraphPad Prism™] GRAPHPAD PRISM™ 2.0a (GraphPad Software Inc.). --

Please amend the second paragraph under Example 7 on page 91 as follows:

-- A modified [Flash Plate™] FLASH PLATE™ Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) is preferably utilized for confirmation of candidate compounds directly identified as inverse agonists and agonists to non-endogenous, constitutively activated GPCR in accordance with the following protocol. --

Please amend the paragraph bridging pages 91 and 92 as follows:

-- Transfected cells will be harvested approximately three days after transfection. Membranes are prepared by homogenization of suspended cells in buffer containing 20mM HEPES, pH 7.4 and 10mM $MgCl_2$. Homogenization is performed on ice using a Brinkman [Polytron™] POLYTRON™ for approximately 10 seconds. The resulting homogenate will be centrifuged at 49,000 X g for 15 minutes at 4°C. The resulting pellet is then resuspended in buffer containing 20mM HEPES, pH 7.4 and 0.1 mM EDTA, homogenized for 10 seconds, followed by centrifugation at 49,000 X g for 15 minutes at 4°C. The resulting pellet can be stored at -80°C until utilized. On the day of direct identification screening, the membrane pellet is slowly thawed at room temperature, resuspended in buffer containing 20mM HEPES, pH 7.4 and 10mM $MgCl_2$, to yield a final protein concentration of 0.60mg/ml (the resuspended membranes are placed on ice until use). --

Please amend the last paragraph on page 93 as follows:

-- Following the incubation, 100µl of Detection Buffer is added to each well, followed by incubation for 2-24 hours. Plates are then counted in a Wallac [MicroBeta™] MICROBETA™ plate reader using "Prot. #31" (as per manufacturer instructions). --

In the Claims

Please amend claim **103** to read as follows:

103. (Amended Once) A method for directly identifying a non-endogenous compound as a compound having an activity selected from the group consisting of: inverse agonists, [parallel] agonists, and partial agonists, to a non-endogenous, constitutively activated version of known G protein-coupled receptor, said receptor comprising a transmembrane-6 region and an intracellular region, comprising the steps of:

(a) selecting a non-endogenous version of a known GPCR;

(b) confirming that the selected non-endogenous GPCR of step (a) is constitutively active;

(c) contacting a non-endogenous candidate compound with the non-endogenous, constitutively activated GPCR of step of (b); and

(d) determining, by measurement of the compound efficacy at said contacted receptor, whether said non-endogenous compound [having inverse agonist activity] is [as] an inverse agonist, an agonist, or a partial [is an] agonist to said receptor of step (b).